Lack of prevention of heart failure by serial electrical cardioversion in patients with persistent atrial fibrillation

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Abstract

***Objective*—To investigate the occurrence of heart failure complications, and to identify variables that predict heart failure in patients with (recurrent) persistent atrial fibrillation, treated aggressively with serial electrical cardioversion and antiarrhythmic drugs to maintain sinus rhythm.**

***Design*—Non-randomised controlled trial; cohort; case series; mean (SD) follow up duration 3.4 (1.6) years.**

***Setting*—Tertiary care centre.**

***Subjects*—Consecutive sampling of 342 patients with persistent atrial fibrillation (defined as > 24 hours duration) considered eligible for electrical cardioversion.**

***Interventions*—Serial electrical cardioversions and serial antiarrhythmic drug treatment, after identification and treatment of underlying cardiovascular disease.**

***Main outcome measures*—heart failure complications: development or progression of heart failure requiring the institution or addition of drug treatment, hospital admission, or death from heart failure.**

***Results*—Development or progression of heart failure occurred in 38 patients (11%), and 22 patients (6%) died from heart failure. These complications were related to the presence of coronary artery disease ($p < 0.001$, risk ratio 3.2, 95% confidence interval (CI) 1.6 to 6.5), rheumatic heart disease ($p < 0.001$, risk ratio 5.0, 95% CI 2.4 to 10.2), cardiomyopathy ($p < 0.001$, risk ratio 5.0, 95% CI 2.0 to 12.4), atrial fibrillation for < 3 months ($p = 0.04$, risk ratio 2.0, 95% CI 1.0 to 3.7), and poor exercise tolerance (New York Heart Association class III at inclusion, $p < 0.001$, risk ratio 3.5, 95% CI 1.9 to 6.7). No heart failure complications were observed in patients with lone atrial fibrillation.**

***Conclusions*—Aggressive serial electrical cardioversion does not prevent heart failure complications in patients with persistent atrial fibrillation. These complications are predominantly observed in patients with more severe underlying cardiovascular disease. Randomised comparison with rate control treatment is needed to define the optimal treatment for persistent atrial fibrillation in relation to heart failure.**

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Keywords: atrial fibrillation; cardioversion; heart failure

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Atrial fibrillation is the most common cardiac arrhythmia, with an estimated prevalence of up to 0.89% in the general population.[1–3] Its incidence increases strongly with age and with the presence of cardiovascular disease.[1 4 5] The relative risk on the development of heart failure during atrial fibrillation in large cohort studies is approximately threefold.[1 5] Conversely, in patients with more advanced heart failure, atrial fibrillation is a common concomitant disorder,[6–9] but the impact of atrial fibrillation on mortality in patients with moderate to severe heart failure is still uncertain.[6 7 10] These data, however, pertain to "general" atrial fibrillation, for which treatment is not specified. At present, it is unknown whether patients with persistent atrial fibrillation treated intensively with serial electrical cardioversion and serial antiarrhythmic drugs (which is still common practice), with the intention of maintaining sinus rhythm, also show heart failure complications. This may be important, as recent data suggest that the arrhythmia prognosis is relatively poor with such an approach, especially in those already suffering from heart failure,[11] favouring acceptance of atrial fibrillation earlier during the course of the disease. However, such a decision should be guided not only by arrhythmia outcome, but also by morbidity and mortality in relation to the therapeutic strategy adopted. Our aim in this study was therefore to investigate the occurrence of heart failure complications during long term follow up in patients suffering from (recurrent) persistent atrial fibrillation who were treated intensively with serial electrical cardioversion and serial antiarrhythmic drugs to maintain sinus rhythm. In addition, we also investigated clinical variables predicting heart failure during the course of (recurrent) persistent atrial fibrillation.

Methods

STUDY POPULATION

In the course of seven years (January 1986 to January 1993) 426 consecutive patients with persistent atrial fibrillation were referred to our hospital for treatment and included in our prospective cardioversion database. Neither age

nor previous arrhythmia duration were exclusion criteria for participation in the study. Exclusion criteria were New York Heart Association (NYHA) class IV for exercise tolerance (60), unstable angina pectoris (10), and acute myocardial infarction less than four weeks previously (14). The remaining 342 patients constituted the present study group, from which subsets (with more stringent criteria with respect to arrhythmia history) have been described previously.[11–14] The study was approved by the institutional review board.

SERIAL ELECTRICAL CARDIOVERSION

The protocol has been described before.[11–15] In short, electrical cardioversion was the principal treatment of atrial fibrillation, after treatment of any present underlying cardiovascular disease (see section on treatment of underlying cardiovascular disease below). In case of failure to re-establish sinus rhythm with serial electrical cardioversion, the rate control alternative was adopted. All cardioversions were performed on an elective basis. Patients received warfarin or another coumarin at least four weeks before the procedure. If the international normalised ratio (INR) on admission was below 2.4 (see section on anticoagulant treatment below), the cardioversion procedure was postponed for another four weeks.

Electrical cardioversion was performed without antiarrhythmic drug pretreatment. A calibrated Hewlett Packard 43120-A defibrillator (Hewlett Packard Inc, Andover, Massachusetts, USA) which could store 360 joules of energy was used as the cardioverter device. According to the protocol, we started with 50 joules of stored energy. Thereafter, energy load of successive shocks was doubled until sinus rhythm was restored or after two attempts with 360 joules. Post-shock rhythm monitoring was secured by telemetry for eight to 24 hours.

If after the first electrical cardioversion procedure sinus rhythm was accomplished, patients did not receive an antiarrhythmic drug. If atrial fibrillation relapsed, electrical cardioversion was repeated as soon as possible. Those patients who clearly felt that the recurrence of atrial fibrillation lasted less than 24 hours underwent cardioversion without preceding anticoagulation; the others were given warfarin (or another coumarin) for at least four weeks.

Patients with successive arrhythmia recurrences were treated consecutively with three different antiarrhythmic drugs (serial prophylactic antiarrhythmic drug strategy). Until 1989 we used flecainide as the initial agent but because of the results of the cardiac arrhythmia suppression (CAST) trial,[16] we changed our preference to sotalol (160 to 320 mg daily), followed by flecainide (200 to 300 mg daily), and finally amiodarone (600 mg daily for four weeks followed by 200 to 300 mg daily). Both flecainide and sotalol were started during 24 hour telemetric rhythm monitoring. After 1989, the use of flecainide was discontinued in patients with ischaemia, previous myocardial infarction, impaired left ventricular function, and moderate to severe valvar heart disease. Amiodarone was given four weeks or more before repeated electrical cardioversion.

Patients with a relapse of atrial fibrillation after more than one year of sinus rhythm, a so called late recurrence, underwent electrical cardioversion without the subsequent use of prophylactic antiarrhythmic drugs or without change in the antiarrhythmic drug in use at the time. Patients in whom a particular antiarrhythmic drug was contraindicated proceeded to the next agent in the sequence. Inclusion in the study began on the day of the first cardioversion and follow up was completed at death or 1 January 1994, whichever came first. Follow up was at least one year in all patients.

Conditions for acceptance of atrial fibrillation included failure of response to amiodarone, drug related side effects, completely asymptomatic arrhythmia recurrence after (multiple) cardioversion, or refusal to undergo another electrical cardioversion. In these patients, control of the ventricular response to atrial fibrillation was pursued by digitalis and if necessary with additional verapamil, diltiazem, or a β blocker, with the aim of obtaining a resting heart rate under 100 beats/min. Additionally, 24 hour ambulatory ECG (Holter) monitoring was performed to control ventricular rate during daily activity and was repeated after adjustment of rate control treatment. His bundle ablation with implantation of a pacemaker was offered to the patient if symptoms of palpitations were severe or in case of progression or persistence of tachycardia related heart failure.

ANTICOAGULANT TREATMENT

Anticoagulant treatment with dose adjusted warfarin or another coumarin was initiated at least four weeks before (re-)cardioversion and continued after restoration of sinus rhythm for at least four weeks. In the event that atrial fibrillation persisted, and in patients who required prolonged anticoagulation for other indications (for example, mitral valve stenosis), anticoagulant treatment was continued. During treatment, the target INR was 2.4 to 4.8. Anticoagulation was monitored at a regional centre of the Dutch Thrombosis Services, which specialise in monitoring coumarin treatment in outpatients.

TREATMENT OF UNDERLYING CARDIOVASCULAR DISEASE

Before acceptance for serial electrical cardioversion, any underlying disease was treated as adequately as possible according to clinical practice at that time (see below). Patients suffering from hyperthyroidism were only included after at least three months of adequate treatment.

Treatment of ischaemic heart disease

Ischaemic heart disease was treated stepwise starting with a β blocker, and then adding a calcium channel blocker and/or nitrates. When contraindications or adverse drug effects were present, other combinations were prescribed. Surgical intervention for ischaemic heart

Table 1 Baseline characteristics of the 342 patients

Characteristic	*All patients*
Male/female (n)	188/154
Age (years) (mean (SD))	62 (12)
< 57	89 (26)
57–64	72 (21)
64–71	92 (27)
⩾ 71	89 (26)
Underlying heart disease*	
Coronary artery disease	84 (25)
Rheumatic heart disease	70 (21)
Mitral valve disease, non-rheumatic	28 (8)
Aortic valve disease, non-rheumatic	22 (6)
Hypertension	58 (17)
Dilated cardiomyopathy	26 (8)
Other aetiology†	60 (18)
Lone AF	69 (20)
Duration of AF (months) (median (range))	9 (0.1 to 420)
< 3	79 (23)
3–9	89 (27)
9–36	80 (24)
⩾ 36	87 (26)
Previous AF episodes (mean (SD))	2 (1)
NYHA class I/II/III	112/155/75 (33/45/22)
Left atrial size (mm) (mean (SD))	46 (8)
LVEDD (mm) (mean (SD))	52 (8)
LVESD (mm) (mean (SD))	37 (9)
Fractional shortening (mean (SD))	0.30 (0.09)

Values are n (%) unless otherwise stated.
*More than one underlying disease per patient was scored.
†Patients with chronic obstructive pulmonary disease and hyperthyroidism.
AF, atrial fibrillation; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; NYHA, New York Heart Association.

disease was considered, and if feasible performed, when antianginal drugs became ineffective.

Treatment of heart failure
After data from studies on the efficacy of angiotensin converting enzyme (ACE) inhibitors became available, all patients with impaired left ventricular function were treated with ACE inhibitors with or without digoxin and diuretics.

Table 2 Characteristics at baseline of patients who developed a heart failure complication versus those without a heart failure complication

Characteristic	*Complication*	*No complication*	*p Value‡*
Numbers of patients	45	297	
Male/female (n)	26/19	162/135	0.75
Age (years) (mean (SD))	61 (10)	65 (12)	0.22
Underlying heart disease*			
Coronary artery disease	17 (38)	67 (23)	0.04
Rheumatic heart disease	18 (40)	52 (18)	< 0.001
Mitral valve disease	1 (2)	27 (9)	0.15
Aortic valve disease	2 (4)	20 (7)	0.75
Hypertension	4 (9)	54 (18)	0.14
Cardiomyopathy	9 (20)	16 (5)	< 0.001
Other aetiology†	9 (20)	51 (17)	0.67
Lone AF	0 (0)	69 (23)	< 0.001
Duration AF (months) (median (range))	8 (0.1 to 192)	9 (0.1 to 420)	0.89
< 3 months	15 (35)	64 (22)	0.08
3–9 months	7 (16)	82 (28)	0.14
9–36 months	7 (16)	73 (25)	0.25
⩾36 months	14 (33)	73 (25)	0.35
Previous AF episodes (n) (mean (SD))	2 (1)	4 (1)	0.98
NYHA class I/II/III	7/16/22 (16/36/48)	105/139/53 (35/47/18)	< 0.001
Left atrial size (mm) (mean (SD))	50 (9)	46 (7)	0.01
LVEDD (mm) (mean (SD))	56 (9)	51 (8)	< 0.001
LVESD (mm) (mean (SD))	43 (11)	36 (9)	< 0.001
Fractional shortening (mean (SD))	0.25 (0.10)	0.30 (0.09)	0.01

Values are n (%) unless otherwise stated.
*More than one underlying disease per patient was scored.
†Patients with chronic obstructive pulmonary disease and hyperthyroidism.
‡Univariate p value.
AF, atrial fibrillation; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; HF complication, heart failure event (development or progression), or heart failure death; NYHA, New York Heart Association.

Treatment of hypertension
Calcium channel blockers, diuretics, β blockers, or ACE inhibitors were prescribed alone, or in combination, to achieve a systolic blood pressure < 160 mm Hg and a diastolic blood pressure < 95 mm Hg.

Treatment of valve disease
Patients with aortic or mitral valve disease were treated with diuretics, ACE inhibitors, and/or vasodilators depending on the severity of valve dysfunction and the type of valve disease. Valve replacement or repair was considered whenever symptoms, echocardiographic findings, and cardiac catheterisation data indicated the need for surgical intervention.[17–19]

ECHOCARDIOGRAPHY
All measurements were averaged from three cardiac cycles. Left atrial size (anteroposterior dimension) was obtained from the parasternal long axis view. All measurements were taken at end systole with the inner edge to inner edge convention. Left ventricular diastolic and systolic dimensions were measured in the parasternal long axis view, in accordance with standard recommendations.[20] Fractional shortening was calculated as the difference between end diastolic and end systolic dimensions divided by end diastolic dimension.

FOLLOW UP PROCEDURE
One, three, and six months after discharge, patients were scheduled for outpatient department visits. Thereafter patients were seen every six months. During each visit, the following items were assessed: complaints, rhythm and rhythm history, drug use, NYHA class for exercise tolerance, and complications—for example, thromboembolic events, bleeding events, admission for heart failure. Routinely, it also included a physical examination and a 12 lead ECG. Additional investigations (for example, a 24 hour ambulatory ECG) were performed depending on clinical status. In case of death, data on the circumstances were obtained from hospital records, the treating physician, the family doctor, or a close relative.

DEFINITION OF TERMS
Persistent atrial fibrillation—Documentation of atrial fibrillation on at least two occasions without intercurrent sinus rhythm at consecutive outpatient visits, and continuous presence of atrial fibrillation on a 24 hour Holter recording. Persistent atrial fibrillation has a non-spontaneously converting character and restoration of sinus rhythm is desirable, in contrast to permanent atrial fibrillation when the arrhythmia is accepted and cardioversion is no longer (or not) indicated.[21] Previously, both types of atrial fibrillation were classified as chronic atrial fibrillation.
Successful cardioversion—Maintenance of sinus rhythm by time of hospital discharge—that is, more than eight hours after cardioversion.
Heart failure complication—Development or progression of heart failure during follow up requiring the institution or addition of drug

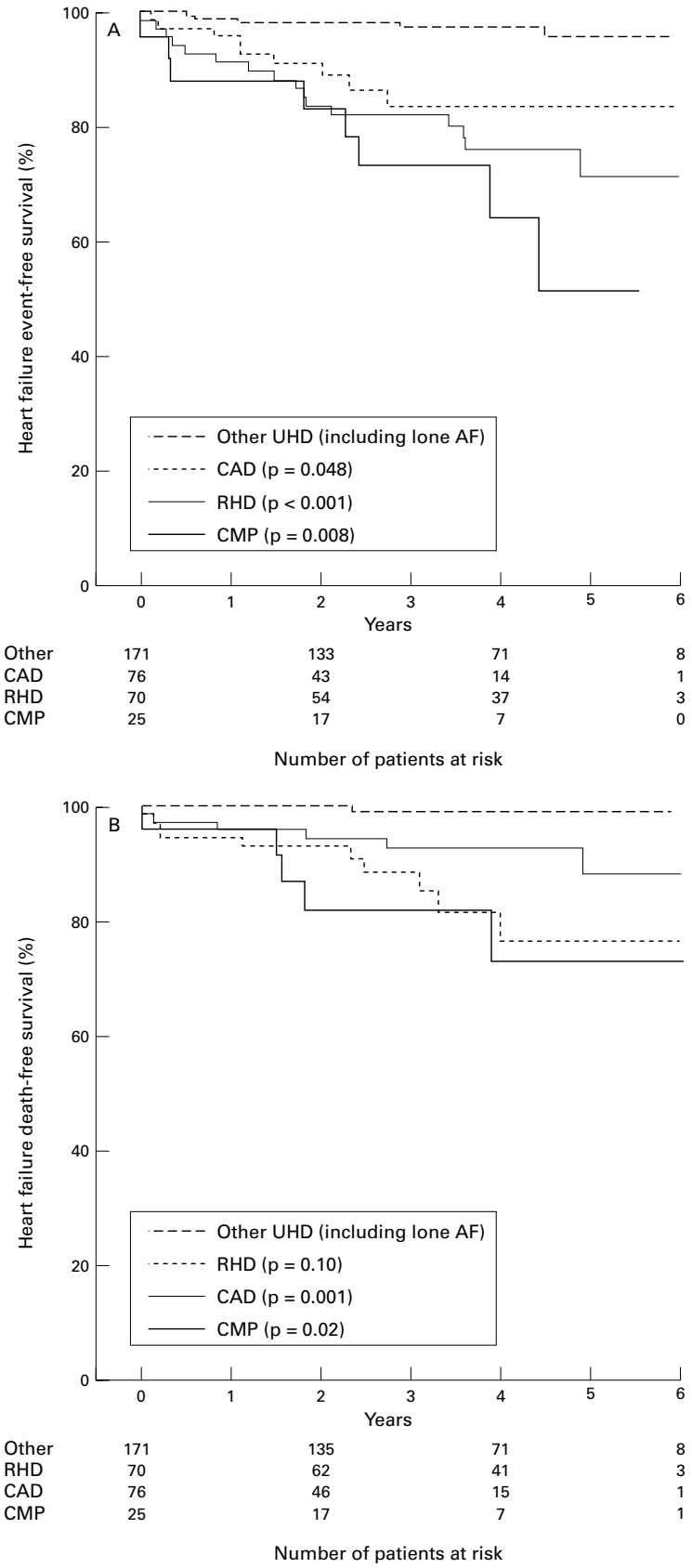

Figure 1 Kaplan–Meier plots showing the probability (A) of heart failure event-free survival (that is, free from the development or progression of heart failure) and (B) of not dying of heart failure, in relation to the type of underlying disease. AF, atrial fibrillation; CAD, coronary artery disease; CMP, dilated cardiomyopathy; HF, heart failure; RHD, rheumatic heart disease; UHD, underlying heart disease.

treatment, or hospital admission, including valve surgery. Also included is death from progressive heart failure.

Death from heart failure—(Rapidly) progressive heart failure leading to death.

DATA ANALYSIS AND STATISTICAL METHODS

For normally distributed variables, values are given as mean (SD). Categorical variables are presented by frequencies and percentages. In case of skewed distribution, the median values and ranges are given. Comparison between groups with normally distributed variables was performed by one way analysis of variance, and skewed variables by the Wilcoxon two sample test. Group comparison for categorical variables was performed by the χ^2 test with continuity correction or Fisher's exact test as appropriate. Univariate Cox regression analysis was used to identify the variables determining event-free survival. Continuous variables were categorised in quartiles, and linearity of the calculated odds ratios with respect to the response was assessed. If no linearity was demonstrated, quartiles with comparable odds ratios were combined. From the univariate Cox regression analysis, variables with p values < 0.20 were selected for the multivariate Cox regression analysis, and relevant first order interactions were tested, using the backward selection method. Survival curves were constructed using the Kaplan–Meier method, and the p values from the Cox multiple analysis are reported in the resulting survival plots. All p values are two sided, and a p value < 0.05 was considered statistically significant. SAS version 6.12 (Cary, North Carolina, USA) was used for all statistical evaluations.

Results

PATIENTS

The baseline characteristics of the 342 study patients are given in table 1. Mean follow up was 3.4 (1.6) years (range 1.0 to 6.9).

HEART FAILURE COMPLICATIONS

Forty five patients (13% of all the patients) suffered from a heart failure complication during follow up; development or progression of heart failure occurred in 38 patients (11% of all patients), and 22 patients died from rapidly progressive heart failure (seven died without previous development or progression of heart failure during follow up). At the time of the heart failure complication, 35 patients (78% of the 45 patients who developed such complications) were in atrial fibrillation after unsuccessful serial electrical cardioversion. Additionally, more than 20 of these 35 patients had a resting heart rate over 100 beats/min when the heart failure complication was observed. In two patients, the occurrence of the heart failure complication was clearly related to acute ischaemia.

The results of the univariate comparison of baseline characteristics of patients with and without a heart failure complication (development or progression of heart failure or death from heart failure during follow up, or both) are given in table 2. Multivariate Cox

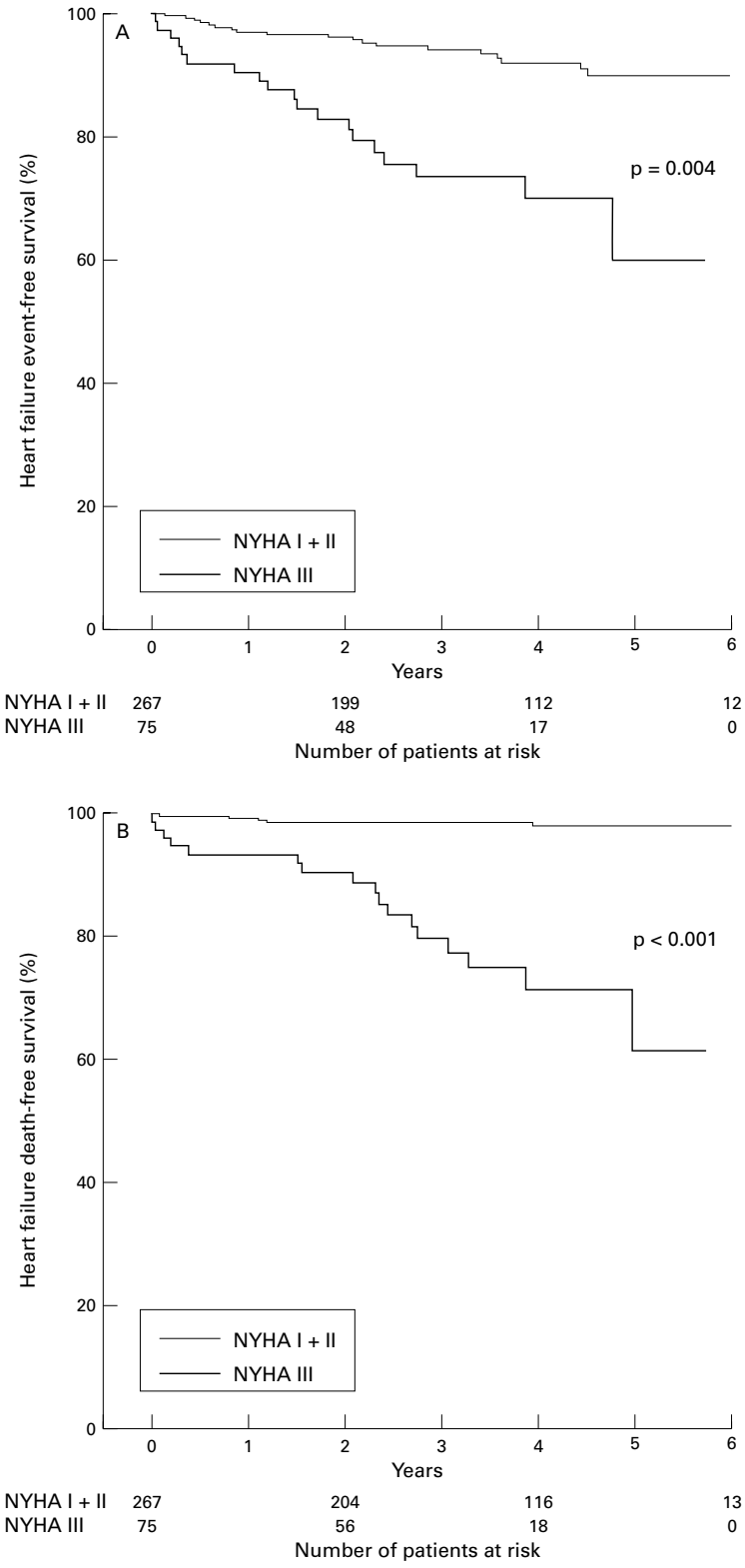

Figure 2 Kaplan–Meier plots showing the probability (A) of heart failure event-free survival (that is, free from the development or progression of heart failure) and (B) of not dying of heart failure, in relation to the functional class for exercise tolerance at inclusion (NYHA class I and II, v NYHA class III). HF, heart failure; NYHA, New York Heart Association.

regression analysis showed also that patients who developed heart failure complications suffered more often from coronary artery disease ($p < 0.001$, risk ratio 3.2, 95% confidence interval (CI) 1.6 to 6.5), rheumatic heart disease ($p < 0.001$, risk ratio 5.0, CI 2.4 to 10.2), or cardiomyopathy ($p < 0.001$, risk ratio 5.0, CI 2.0 to 12.4). Patients who had atrial fibrillation for less than three months had a twofold increased risk of heart failure complications (CI 1.0 to 3.7, $p = 0.04$) compared with those with a duration of more than three months. Finally, patients with a severely impaired exercise tolerance at inclusion (NYHA class III for heart failure compared to class I or II) had a 3.5-fold increased risk of heart failure complications (CI 1.9 to 6.7, $p < 0.001$). In contrast, patients with lone atrial fibrillation were unlikely to develop heart failure during follow up.

Figure 1 shows the probability of survival free from heart failure events—that is, development or progression of heart failure (fig 1A)—or of not dying of heart failure (fig 1B) during follow up, in relation to the underlying disease. Patients with coronary artery disease ($p < 0.048$), rheumatic heart disease ($p < 0.001$), and cardiomyopathy ($p < 0.008$) suffered more often from heart failure (fig 1A) than those with lone atrial fibrillation or other underlying disease. Mortality from heart failure, however, was increased only in patients with coronary artery disease ($p = 0.001$) and cardiomyopathy ($p = 0.02$), but not in patients suffering from rheumatic heart disease (fig 1B).

Figure 2 shows the probability of survival free from heart failure events—that is, development or progression of heart failure (fig 2A)—or of not dying of heart failure (fig 2B) during follow up, in relation to the severity of heart failure at inclusion (NYHA class for exercise tolerance). Patients in functional class III for exercise tolerance at inclusion had a higher risk of either development or progression of heart failure ($p = 0.004$, fig 2A) or death from heart failure ($p < 0.001$, fig 2B) during follow up. Death due to (rapid) progression of heart failure was rare in patients with asymptomatic or mild heart failure at inclusion (functional class I or II).

At the end of follow up, 33 of the 45 patients (73%) who suffered from a heart failure complication during follow up were in atrial fibrillation. In contrast, 184 of the 297 patients (62%) without a heart failure complication were in atrial fibrillation ($p = 0.03$). Figure 3 shows the success of the serial electrical cardioversion strategy in relation to the severity of heart failure at inclusion (fig 3A), and in relation to the occurrence of a heart failure complication during follow up (fig 3B). Both the patients with heart failure at inclusion and those who suffered from heart failure complications during follow up had a worse arrhythmia outcome—that is, no long term maintenance of sinus rhythm.

Only one patient suffered from progression of heart failure related to antiarrhythmic drug use. She started flecainide after successful cardioversion and developed an exacerbation of heart failure one day later. She recovered after discontinuation of flecainide and administration of diuretics. Flecainide was instituted in this patient before the CAST data were published. Her cardiac function was moderately

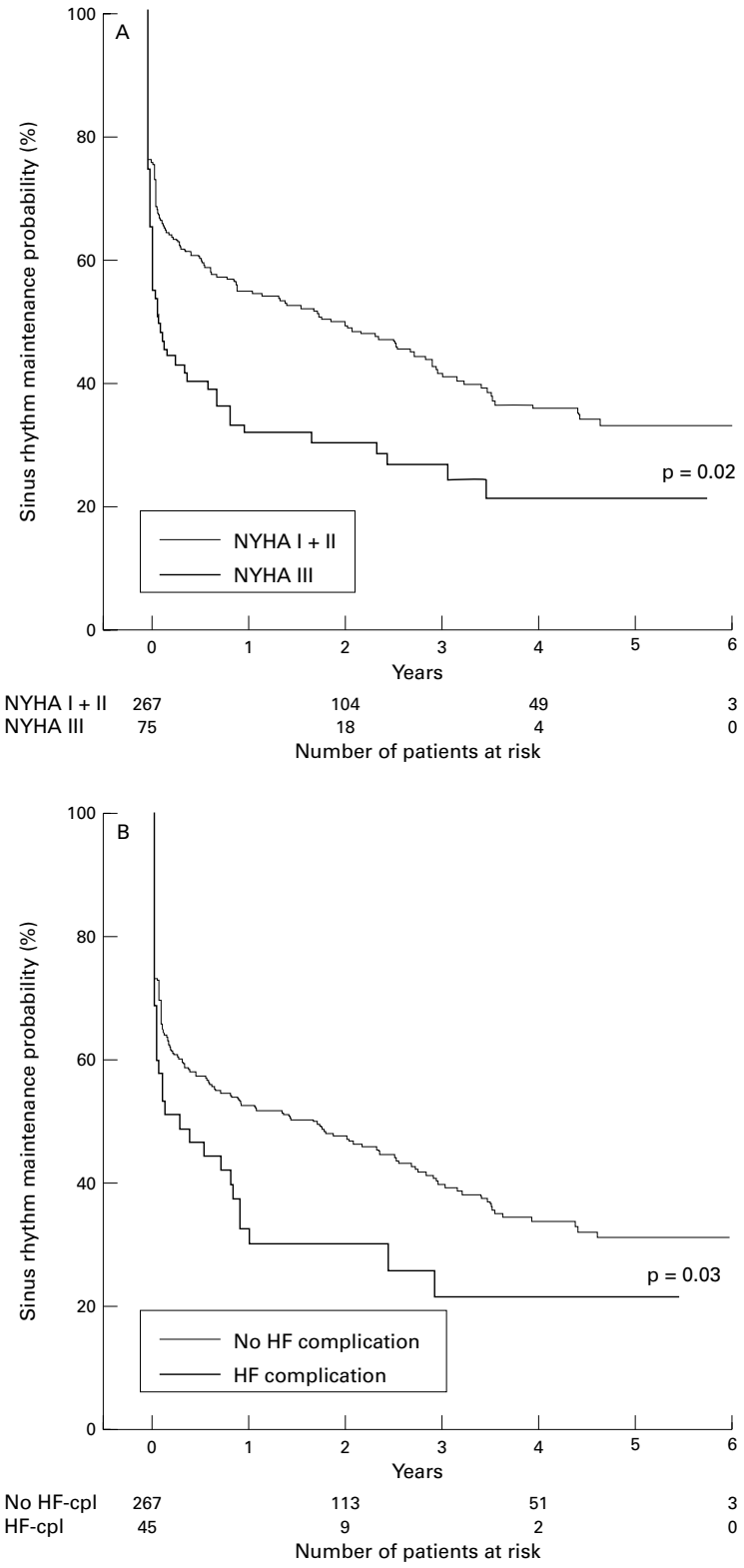

Figure 3 Kaplan–Meier plots, showing the probability of maintenance of sinus rhythm in relation to the severity of heart failure at inclusion (A) and the occurrence of a heart failure complication during follow up (B). HF, heart failure; NYHA, New York Heart Association.

impaired owing to an old anterior myocardial infarct.

Seven patients died of heart failure while on antiarrhythmic drug treatment (amiodarone in all cases). All these patients were suffering from end stage heart failure and were on optimal heart failure treatment, including ACE inhibition, diuretics, and digoxin. Four patients died in hospital and the other three died at home. Although amiodarone related ventricular proarrhythmia cannot be excluded for certain, this was unlikely, given the clear presence of end stage heart failure.

Discussion

Our study showed that in patients with persistent atrial fibrillation, intensive arrhythmia treatment with the intention of maintaining sinus rhythm did not prevent the occurrence of heart failure complications. During follow up, these complications predominantly occurred in patients with more severe underlying cardiovascular disease and those with heart failure at the time of inclusion (NYHA class III for exercise tolerance). In contrast, no heart failure complications occurred in patients with less severe underlying cardiovascular disease—that is, where atrial fibrillation was the principal complaint. Antiarrhythmic drug treatment, as prescribed in the present study, did not seem to be a significant cause of heart failure complications.

Heart failure is a common finding in patients with atrial fibrillation.[1 5 22] In our study group 22% of the patients were suffering from advanced heart failure (NYHA class III) at inclusion. Progression of, and subsequent death from, heart failure was observed mainly in this group, despite an aggressive therapeutic strategy to maintain sinus rhythm. Interestingly, these patients also showed a poor outcome when the serial electrical cardioversion approach was followed. In other words, both the prognosis of the underlying disorder and the outcome of the arrhythmia were unfavourable in these patients. This could be explained by the presence of more severe underlying disease and its deleterious effect on the clinical outcome. In addition, after failure of the serial electrical cardioversion approach and acceptance of atrial fibrillation, inadequate control of ventricular rate[23–26] and the irregularity of the heart rhythm per se[27 28] may have further contributed to depressed haemodynamic function. The occurrence of heart failure in patients with accepted atrial fibrillation was associated with a ventricular rate over 100 beats/min in the majority, but this does not prove which came first—inadequate control of ventricular rate leading to additional ventricular dysfunctioning (that is, tachycardiomyopathy), or the occurrence of heart failure with neurohumoral activation leading to high heart rates. In this respect, we want to emphasise that during follow up 24 hour ambulatory electrocardiography was performed to ensure maintenance of mean heart rates below 100 beats/min in patients with accepted atrial fibrillation.

It is still controversial whether atrial fibrillation independently contributes to increased mortality in heart failure patients, and whether atrial fibrillation is an independent risk factor for sudden death or heart failure death. Recently, it was suggested that survival of heart failure patients with or without atrial fibrillation was comparable,[10] whereas previously a

causal relation between atrial fibrillation and mortality in such patients was suggested.[6] This change was attributed to the more frequent use of amiodarone and angiotensin converting enzyme inhibitors in heart failure patients with atrial fibrillation, instead of class I antiarrhythmic drugs,[6 7 10] which have been associated with excess mortality, especially in the presence of heart failure.[16 29–31] In other words, survival of heart failure patients with atrial fibrillation in general has improved over recent years, confirming the view that the correct treatment of the underlying cardiovascular disease is of greater importance than the treatment of the atrial fibrillation.[32] In line with these data are our present findings showing that progression of heart failure and death from heart failure occur predominantly in patients with more severe underlying disease or heart failure at entry to the study.

While patients suffering from coronary artery disease, rheumatic heart disease, and dilated cardiomyopathy all developed heart failure, only those with coronary artery disease and dilated cardiomyopathy had a higher mortality. This is probably related to successful surgical treatment in cases of severe valve disease. Unfortunately, heart failure induced by coronary artery disease or dilated cardiomyopathy is progressive, and there are only limited prospects for treatment at present.

In the present study, progression of heart failure and heart failure death could not be related to antiarrhythmic drug use; this probably reflects our prudent prescription of class IC drugs and in-hospital initiation of antiarrhythmic drug treatment.[33] Only one patient developed heart failure after initiation of flecainide treatment, and this resolved after flecainide was discontinued. In addition, we did not prescribe class IA drugs, such as quinidine, which may also have harmful effects.[29 34]

Lone atrial fibrillation was not associated with heart failure or with death from heart failure. Our present data compare favourably with those on patients with lone atrial fibrillation in the Framingham study,[35] and with the study of Kopecky *et al*.[36] This implies that atrial fibrillation in the setting of no or only minor heart disease is a relatively benign condition with respect to heart failure and mortality.

Unexpectedly, atrial fibrillation of short duration (less than three months) was associated with heart failure complications. Perhaps this relates to the fact that the development of atrial fibrillation in the setting of heart failure may be a consequence of worsening haemodynamics,[6] which in turn may cause further deterioration in the clinical and haemodynamic situation.[9]

LIMITATIONS OF THE STUDY

This non-randomised study did not compare the cardioversion strategy with the rate control strategy in patients with persistent atrial fibrillation and heart failure. Such a comparison might have determined whether cardioversion treatment could be omitted in patients who have a poor success rate with cardioversion. However, our data suggest that instead of cardioversion as a first line measure, treatment should focus on the underlying cardiovascular disease. Ongoing randomised studies comparing both strategies might answer this latter question.[37 38] Furthermore, we did not thoroughly investigate the effect of inadequate control of ventricular rate (particularly during exercise) on the development of tachycardiomyopathy in patients with atrial fibrillation, although ventricular rate was controlled as far possible using 24 hour ambulatory electrocardiography.

Finally, the question of what is the optimal antiarrhythmic drug for preventing atrial fibrillation in patients with heart failure cannot be answered from our study. The benefit of serial antiarrhythmic drugs on the maintenance of sinus rhythm seems limited, especially in patients with heart failure. Amiodarone might be a good first line antiarrhythmic drug in heart failure patients, but this remains to be proven.

CLINICAL IMPLICATIONS

Our data indicate that the application of serial electrical cardioversion neither prevents heart failure complications nor is very successful in restoring and maintaining sinus rhythm. These findings suggest that the rate control strategy would be a suitable alternative, but a randomised comparison of both strategies is needed to draw more definite conclusions. We are therefore eagerly awaiting data from studies randomising patients to either serial electrical cardioversion or rate control therapy, such as the AFFIRM[37] and PIAF studies[38] and the RACE study (currently underway in the Netherlands). These studies are likely to answer the question of whether the rate control strategy might be adopted earlier in patients with atrial fibrillation in the setting of heart failure and underlying disease.

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